Remote Ischaemic Conditioning for Fatigue After Stroke 2 (RICFAST 2) –

A multi-arm, randomised controlled feasibility trial

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This document describes a clinical trial and provides information about procedures for entering participants.

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Abbreviations

6MWT	Six Minute Walk Test
ADL	Activities of Daily Living
AE	Adverse Event
ARC	Assessment and Rehabilitation Centre
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BI	Barthel Index
CI	Chief Investigator
CIs	Confidence Intervals
CONSORT	Consolidated Standards of Reporting Trials
CPET	Cardiopulmonary exercise testing
CRF	Case Report Form
CST	Consent Support Tool
DPA	Data Protection Act
EDI	Equality, Diversity and Inclusion
EQ-5D	Euroqol-5D
FFS-7	Fatigue Severity Scale
GAD-7	General Anxiety Disorder Assessment
GCP	Good Clinical Practice
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISDN	Integrated Stroke Delivery Networks
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials
LPLV	Last Participant Last Visit
MCID	Minimum Clinically Important Difference
MFIS	Modified Fatigue Impact Scale
MRI	Magnetic Resonance Imaging
mNIHSS	Modified National Institute of Health Stroke Scale
mRS	Modified Rankin Scale

NIHR	National Institute for Health Research
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NIHSS	National Institute of Health Stroke Scale
PHQ-9	Patient Health Questionnaire
Pi	Inorganic Phosphate
PI	Principal Investigator
PIS	Participant Information Sheet
PSF	Post Stroke Fatigue
QoL	Quality of Life
RCT	Randomised Control Trial
REC	Research Ethics Committee
RIC	Remote Ischaemic Conditioning
SAE	Serious Adverse Event
SD	Standard Deviation
SIG	Sheffield Stroke and Aphasia Group
SSNAP	Sentinel Stroke National Audit Programme
SIS	Stroke Impact Scale
TMF	Trial Master File
TMG	Trial Management Group
VO2peak	Peak VO2
VAT	Ventilatory Anaerobic Threshold
VO2/VCO2	VO2/VCO2 slope

1· General information

1.1 Investigator details

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1.3 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.4 Trial Summary

Trial title	**RICFAST 2 – Re**mote Ischaemic **C**onditioning for **Fa**tigue after **St**roke
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	The Stroke Association
ISRCTN	
Project start date	01/11/2024
Project end date	31/10/2027
Hypothesis, aims and objectives	Aims: To investigate the safety, tolerability and feasibility of differing treatment schedules of RIC in PSF and to understand mechanisms of action. Specific primary objectives: 1.) Determine whether RIC self-delivered at home is feasible at a frequency of 3 times weekly for 6 weeks, 5 times weekly for 6 weeks, or 3 times weekly for 12 weeks. *Hypothesis 1: Participants in all treatment groups will find self-delivery of the intervention at home feasible.* 2.) Determine whether an increased dose (frequency or duration of therapy) of RIC results in greater and more sustained improvement in PSF. *Hypothesis 2: Participants who undergo more intense or longer RIC will experience greater improvements in fatigue severity than in control or the regular RIC group.* 3.) Determine whether any benefits of RIC on fatigue are sustained beyond the end of treatment. *Hypothesis 3: The beneficial effects of RIC will be sustained at 24 weeks* from the start of treatment*, particularly in the prolonged treatment group (12 weeks RIC).* 4.) Determine whether the effects of RIC occur through alterations in tissue ATP metabolism and improved anaerobic endurance.

	Hypothesis 4: RIC will result in increased levels of resting state muscle ATP as determined by MRI spectroscopy and an increased anaerobic threshold as determined by CPET. 5.) Determine if people with PSF have a predominant phenotype or symptoms characteristic profile using fatigue screening tools. *Hypothesis 5: People with PSF may differ according to symptom characteristics, with some experiencing predominantly physical, cognitive or psychosocial symptoms.* 6.) To understand how PSF affects markers of physical activity using smart wearable devices. *Hypothesis 6: Those with more severe fatigue exhibit lower levels of physical activity e.g. step count, move calories.*
Trial design	Single blind, randomised, controlled, 4-arm trial with blinded outcome assessment. Participants will be randomised 1:1:1:1 to one of the four treatment groups.
Setting	Sheffield Teaching Hospitals receiving referrals from South Yorkshire (Doncaster, Rotherham, Barnsley)
Participants	A total of 60 participants (15 per group). <u>Inclusion Criteria:</u> ● Adults (≥ 18 years) with ischaemic or haemorrhagic stroke, at least 12 weeks prior ● Symptoms of debilitating fatigue for at least 6 weeks (mean FSS ≥ 4). ● Capacity to give informed consent. ● Ability to comply with study procedures (see page 19) <u>Exclusion Criteria:</u> ● Participation in another intervention trial ● Significant peripheral vascular disease, neuropathy, ulceration or lymphadenopathy in the upper limbs

	● Hospitalisation for cardiovascular or cerebrovascular disease within the last 4 weeks (this may act as an ischaemic conditioning stimulus) ● Known causes of fatigue e.g. obstructive sleep apnoea, depression, active thyroid disease, active cancer, MS, MND and PD ● Severe aphasia or cognitive impairment that would preclude their understanding of learning to self-deliver the RIC intervention or complete the required outcome measures (e.g. MRI, exercise tests, questionnaires). We will use the Consent Support Tool (CST) to aid this judgement [ref]. ● Pregnant or trying to get pregnant* ● Prior use of RIC For all participants entering the mechanistic sub-study only: ● Contraindications to Magnetic Resonance Imaging (MRI) (e.g., metal implant), ● Has previously experienced or is likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination.
Intervention & control groups	Participants will be randomised 1:1:1:1 to one of the four trial groups: A. Treatment Group A - Control or Sham group – RIC inflation pressure 50 mmHg 3 x weekly for 6 weeks B. Treatment Group B – Regular RIC group – RIC inflation pressure 200 mmHg 3 x weekly for 6 weeks C. Treatment Group C - Intense RIC group – RIC inflation pressure 200 mmHg 5 x weekly for 6 weeks D. Treatment Group D – Long RIC group – RIC inflation pressure 200 mmHg 3 x weekly for 12 weeks
Primary outcome(s)	<u>Primary Outcome Measure:</u> Feasibility measures: ● Safety ● Acceptability ● Compliance ● Trial feasibility

Secondary outcome(s)	<u>Secondary Outcomes (each measured at 6, 12 and 24 weeks</u> the start of treatment<u>):</u> Compared to baseline, changes in: 1. FSS-7 2. MFIS 3. BI 4. mRS 5. GAD-7 6. PHQ-9 7. SIS 8. EQ-5D 9. 6MWT* 10. Daily step count, sedentary times, exercise time, total estimated sleep time/night * not measured at the 6 month time point Mechanistic evaluation (changes between baseline and 6 weeks): 11. ($\dot{V}O_2$peak), VAT and the $\dot{V}E/VCO_2$ slope 12. Muscle resting state ATP (MR Spectroscopy) 13. Inflammatory markers: - IL-1B - IL-6 - IL-10 - TNF-a - HSP - GLP-1 <u>Safety outcomes</u> Safety will be assessed through recording adverse events (AEs) and serious adverse events (SAEs) experienced throughout the trial. <u>Qualitative outcomes</u> Semi-structured interviews with at least 12 participants exploring experiences of RIC during the trial.
Duration of recruitment period and first enrolment date	30-month recruitment period. Recruitment is expected to run from January 2025 – June 2027.
Duration of follow-up	There will be a 6-month follow-up period after recruitment ends. The total follow-up period is expected to run from April 2024 – November 2027.

Target sample size	The trial will require 60 participants in total (15 per group with outcome data at 12 weeks).
Definition of end of trial	The end of the trial is defined as completion of the 6-month follow-up for the last participant (last participant, last visit (LPLV).

2. Introduction

2.1 Background

Post stroke fatigue (PSF) is the feeling of exhaustion that persist seven after rest and affects over 50% of stroke survivors during their recovery [1], half of whom report it as one of their worst symptoms [2-4]. Stroke survivors and clinicians report fatigue as a key limitation in post-acute rehabilitation [5], while longer-term it impairs functional recovery [2], social engagement, return to work, and is associated with reduced quality of life [6]. Identifying effective treatments for PSF has been highlighted as the fourth main priority for life after stroke research nationally [7] and internationally [8].

PSF may be due to alterations in cortico-motor excitability [9], elevated levels of inflammation [10,11], as well as psychosocial factors [12]. There is however mounting evidence implicating perturbations in mitochondrial function and cellular bioenergetics as a cause of fatigue in several clinical conditions including PSF. Impaired mitochondrial energy metabolism has been demonstrated in cancer related fatigue [13], chronic fatigue syndrome [14], and in neurological conditions with very high prevalence of fatigue including motor neurone disease (MND) [15], and Parkinson's disease (PD) [16]. Reduced muscle mitochondrial enzyme content has been demonstrated in severely fatigued elderly compared to non-fatigued counterparts [17] **and impaired aerobic energy metabolism has been shown in mitochondria of people with PSF [18]**. Thus, addressing mitochondrial function is likely to be a critical component in the management of PSF.

2.2 Rationale for current trial

RIC as a potential therapeutic for PSF

Remote Ischaemic Conditioning (RIC) imparts brief and reversible episodes of ischaemia and reperfusion cyclically to an arm by inflating and deflating a blood pressure cuff to greater than systolic pressures. RIC has been shown to improve cerebral blood flow in preclinical models [19] as well as in clinical studies of vascular cognitive impairment [20] and stroke [21], potentially important in the context of altered cortico-motor excitability in PSF. The release of vasoactive substances (nitrous oxide, adenosine) in response to RIC has been shown to improve endothelial reactivity and skeletal muscle perfusion in healthy human participants [22,23] which may mitigate the impairment in sustained muscle contraction seen in post stroke muscle fatigue [24]. Further, RIC may moderate the inflammatory component of PSF through its effects on reducing inflammatory mediators such as TNF-a, IL-1B, and IL-6 [25]. Most importantly perhaps, animal studies indicate 7 different cellular pathways through which RIC may **preserve mitochondrial oxidative capacity** [26]. In particular, RIC in mice can **preserve mitochondrial respiratory chain function** in the brain [27] and slows ATP depletion in porcine skeletal muscle following experimental ischaemic stress [28]. In a clinical population of 22 stroke survivors Durand et al demonstrated that delivery of RIC for 2 weeks significantly increased the duration of submaximal isometric paretic knee extension compared to sham [29], while we have recently demonstrated that RIC can increase walking speeds and distances in people with Multiple Sclerosis (MS) [30]. These multi-modal effects make RIC a compelling therapeutic candidate for PSF, particularly given its effects on bio-cellular energetics.

We recently completed a preliminary randomised controlled trial (RCT) evaluating the safety and tolerability of RIC for PSF (RICFAST Study

NCT03794947) [31]. Twenty-four participants with debilitating PSF (Fatigue Severity Scores (FSS) ≥ 4) were randomised to either RIC (n=12) (arm BP cuff inflation to 200 mmHg for 5 minutes followed by 5 minutes of deflation), or sham (n=12) (cuff inflation pressure 20 mmHg), repeated 4 times, 3 times per week for 6 weeks. Half of the participants self-delivered these interventions at home (during COVID pandemic). Although numbers were small, **RIC was safe and well tolerated with excellent adherence** using this protocol of treatment **(91% sessions completed)**. Although not powered to detect statistical differences in fatigue, there was a strong signal for lower fatigue scores in the RIC group compared to sham (adjusted between group mean difference of -0.7, 95% CI -2.0 to 0.6 at 6 weeks) that persisted at 6 months (-0.9, 95% CI -2.0 to 0.2). These differences are similar to the clinically important difference (CID) for the FSS seen across clinical populations including stroke (0.5 to 1.2) [31]. Improved between group 6-minute walking distances (+43.8m 95%CI -6.0 to 93.6) and ventilatory anaerobic thresholds in RIC participants potentially indicate increased capacity for aerobic (efficient) adenosine triphosphate (ATP) metabolism. Phosphorous-31 MRI spectroscopy (P31 MRS) of the tibialis anterior in 8 participants (4 RIC:4 sham) demonstrated increased levels of resting ATP in all RIC participants while resting ATP levels in sham participants fell. These findings, in conjunction with existing literature described above, **support the concept that RIC is a promising treatment for PSF.**

2.3 Research question

Our main research question is:

Is a more intense and longer RIC intervention for PSF feasible and do they appear to be promising treatments for PSF?

3. Aims and objectives

3.1 Aim

To investigate the safety, tolerability and feasibility of differing treatment schedules of RIC in PSF and to understand mechanisms of action.

3.2 Objectives and Hypotheses

Specific primary objective:

1.) Determine whether RIC self-delivered at home is feasible at a frequency of 3 times weekly for 6 weeks, 5 times weekly for 6 weeks, or 3 times weekly for 10 weeks.

Hypothesis 1: Participants in all treatment groups will find self-delivery of the intervention at home feasible.

Secondary objectives:

2.) Determine whether an increased dose (frequency or duration of therapy) of RIC results in greater and more sustained improvement in fatigue after stroke.

Hypothesis 2: Participants who undergo more intense or longer RIC will experience greater improvements in fatigue severity than in control or the regular RIC group.

3.) Determine whether any benefits of RIC on fatigue are sustained beyond the end of treatment.

Hypothesis 3: The beneficial effects of RIC will be sustained at 24 weeks from the start of treatment*, particularly in the prolonged treatment group (12 weeks RIC).*

4.) Determine whether the effects of RIC occur through alterations in tissue ATP metabolism and improved anaerobic endurance.

Hypothesis 4: RIC will result in increased levels of resting state muscle ATP as determined by MRI spectroscopy and an increased anaerobic threshold as determined by CPET.

5.) Determine if people with PSF have a predominant phenotype or symptoms characteristic profile using fatigue screening tools.

Hypothesis 5: People with PSF may differ according to symptom characteristics, with some experiencing predominantly physical, cognitive or psychosocial predominance.

6.) Using smart wearable devices, we aim to understand how PSF affects markers of physical activity.

Hypothesis 6: Those with more severe fatigue exhibit lower levels of physical activity e.g. step count, move calories.

4. Trial Design

Phase 2 single-blinded 4-arm-RCT with feasibility measures and blinded outcome assessment (figure 1). Sixty participants will be randomised (1:1:1:1) into one of four treatment groups.

A mechanistic sub-study (see section 12) will explore mechanisms by which RIC may act. This includes whether RIC results in increased levels of resting state muscle ATP and whether this leads to improvements in exercise

measures including anaerobic thresholds and whether it alters levels of inflammatory markers

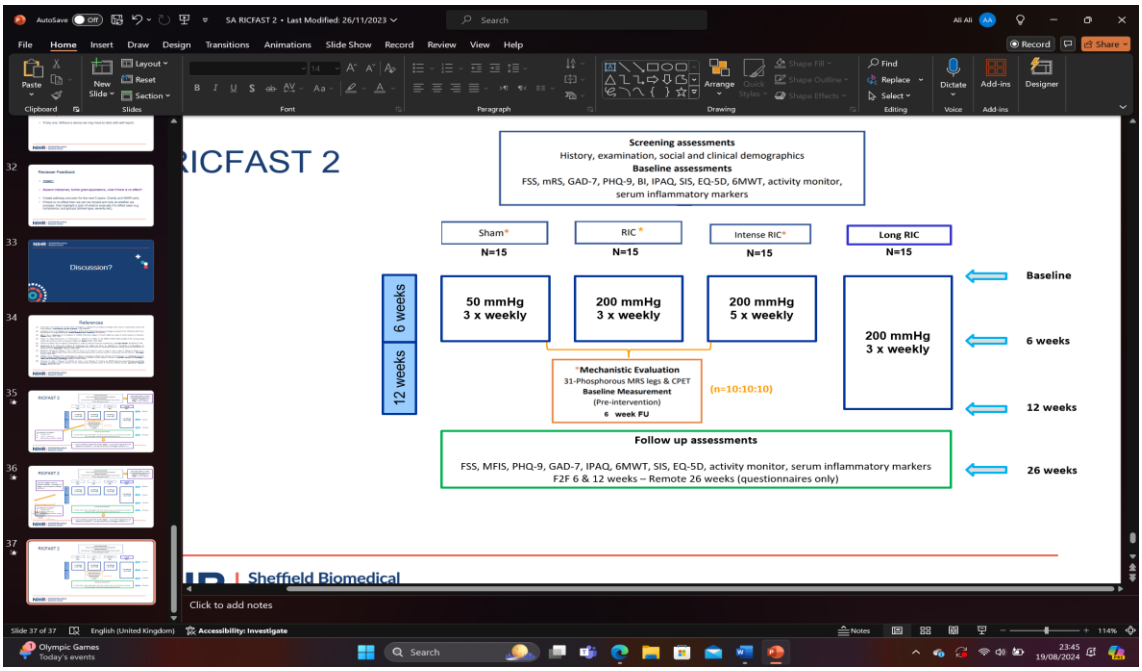


Figure 1. Trial flowchart

5. Selection of participants

The trial population will be participants who have been suffering debilitating PSF who are not participating in any other stroke rehabilitation trial.

5.1 Eligibility criteria

Inclusion Criteria:

- Adults (≥ 18 years) with ischaemic or haemorrhagic stroke, at least 12 weeks prior and no more than 3 years previously

- Symptoms of debilitating fatigue for at least 6 weeks (mean FSS ≥ 4)
- Capacity to give informed consent
- Able to complete study procedures

Exclusion Criteria:

- Participation in another intervention trial
- Significant peripheral vascular disease, neuropathy, ulceration or lymphadenopathy in the upper limbs
- Hospitalisation for cardiovascular or cerebrovascular disease within the last 4 weeks (this may act as an ischaemic conditioning stimulus)
- Known causes of fatigue e.g. obstructive sleep apnoea, depression, active thyroid disease, active cancer, MS, MND and PD
- Severe aphasia or cognitive impairment that would preclude their understanding of learning to self-deliver the RIC intervention or complete the required outcome measures (e.g. MRI, exercise tests, questionnaires). We will use the Consent Support Tool (CST) to aid this judgement [32].
- Pregnant or trying to get pregnant*
- Prior use of RIC

* person of child bearing potential (i.e. fertile following menarche and until becoming post-menopausal, unless permanently sterile) will be asked to perform a pregnancy test to ensure they are not pregnant. They will also only be eligible to participate if they confirm appropriate contraception methods.

For all participants entering the mechanistic sub-study only:

- Contraindications to Magnetic Resonance Imaging (MRI) (e.g., metal implant);
- Has previously experienced or is likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination.

A full screening assessment will be conducted when the participant attends for the MRI to ensure the safety of the participant. For persons of child bearing potential this screening will include the result of the pregnancy test* performed in the initial trial eligibility screen. Potential participants will be advised that they must be willing to use adequate contraception (if appropriate) during the study period.

5.2 Participant identification

Participants will be identified through several possible routes as described below. The adoption of several routes aims to be inclusive and to identify a diverse population.

1) ***Community Stroke Rehabilitation teams (or equivalent)***

We will approach the community stroke rehabilitation (or equivalent) team leads directly in the Sheffield, Doncaster, Rotherham and Barnsley areas, about the trial and disseminate the participant information sheet (PIS) to therapists working with patients who have reported significant fatigue post stroke. Stroke rehabilitation teams will also be asked to identify patients who have previously finished rehabilitation therapy or have not previously had any rehabilitation therapy and still report significant fatigue post stroke.

2) ***The Stroke Association, and relevant local organisations and media***

As well as approaching community teams, we will link with the Stroke Association and advertise the trial on their website. We will put up posters about the trial in community care settings, e.g., in Sheffield there is an Assessment and Rehabilitation Centre (ARC) where patients go if they need ongoing rehabilitation beyond hospital discharge.

We will also harness the new regional stroke networks (Integrated Stroke Delivery Networks, ISDNs). A research active colleague, Dr Jessica Redgrave, is currently the clinical lead. There is a national drive to increase numbers of stroke patients recruited into research trials and there is a fortnightly national community rehabilitation and life after stroke meeting which is attended by rehabilitation therapy leads from all 20 ISDNs in the UK.

To improve representation of underserved groups, information sessions will be run by the central research team to advertise and discuss the trial with community groups where possible e.g. Darnall Wellbeing, SACHMA. As well as widening the potential participant pool this will also build trust between researchers and the local communities.

Potential participants will be provided with an invitation letter and PIS either in person, by email, or post.

Where appropriate, local media or social media may be used to support recruitment, this may include the trial poster or leaflet being shared or an advertisement being placed. This advertisement will be based on information from the approved participant information sheet or leaflet. Contact details will be provided so potential participants can contact the research team.

3) ***Secondary care database searches***

In the South Yorkshire region most patients admitted with acute stroke come to either Sheffield Teaching Hospitals or Doncaster Royal Infirmary and are then repatriated to Rotherham and Barnsley if they are form these areas. We will use our central database to search for patients who have experienced a stroke withing the last 3 years and have consented to be contacted about future research. After eliminating any deceased patients, the locations of the patients

will be mapped geographically so that we can preferentially invite those from areas of higher indices of deprivation and ethnic minority. We will undertake these searches and invitation strategies in waves, reviewing our recruited population characteristics in real time as to amend our invitation targets in subsequent waves.

For this trial, potential participants identified through such database searches will be sent an invitation letter and PIS (either via email or post) along with contact details to enable them to contact the trial team.

4) ***Primary care recruitment***

Once NIHR portfolio adopted, service support costs will help resource infrastructure to search GP databases in Sheffield and South Yorkshire. Expressions of interest will be sent to GP practices inviting them to become participant identification centres (PIC sites). Recruited PIC sites will search GP databases (SystemOne, EMIS) for potentially eligible participants and invitation text messages or emails will be sent to identified individuals with a single follow up message after 4 weeks if no response is received. Test messages and emails will contain a link to the RICFAST trial website or the central research email so potentially interested individuals can contact the central research team.

5.3 Eligibility screening

Upon receiving the PIS, potential participants interested in participating in the trial will be invited to contact the research team (via post, telephone or email) whereupon questions about the trial will be answered and a telephone or video call screening interview will be undertaken to ensure that the participant meets initial eligibility screening (including fatigue assessment). We will also aim to contact those who have not responded to the invitations, at least once, within a

few weeks to ensure we are not excluding those who have difficulty initiating contact. This will include confirming that they have ongoing fatigue following their stroke and that they do not have any clear exclusion criteria. *They will also be given a clear explanation of what participation would involve, including the number of appointments they would be expected to attend and whether they felt they could commit to this.* This explanation will be included at the initial screening stage to ensure that participants are fully aware of the commitment required in an attempt to reduce missed visits and incomplete data at later stages of the trial.

All potential participants who complete the telephone screening interview will be recorded on an anonymised screening form with non-identifiable data. Where potential participants are not interested in the trial, or are ineligible, this will be recorded on the screening form. Participants passing the screening questions will be invited to attend an initial visit to obtain informed consent.

5.4 Informed consent process

Written consent will take place face-to-face in a clinical setting at Sheffield Teaching Hospitals by the principal investigator (PI) or other appropriately trained member of the site research team who has been delegated to conduct this activity. Where possible the participant will provide informed consent, have their eligibility confirmed, baseline data for the main trial collected and randomised in the same visit. However, this may be split into separate visits if required, for example if the participant is fatigued.

For participants with aphasia and for whom the research team are concerned of their ability to adequately understand the standard PIS, the CST [ref] may be used to assess eligibility and whether an accessible PIS, and accessible consent form should be used to aid comprehension. The accessible

versions of the documents have been produced in line with the Stroke Association Accessible Information Guidelines and aim to help support inclusion of participants with aphasia in research studies.

Support for participants with reading difficulties can be provided e.g. audio recordings of patient information sheets and independent witness signature on the consent form.

We will use the CST to help ascertain comprehension ability and eligibility to participate in those with aphasia following stroke. The member of the research team obtaining consent will request verbal consent from the potential participant to conduct part A of the CST [32]. If the potential participant understands fewer than two key written or spoken words in a sentence, they would be considered ineligible as it is unlikely that they will be able to understand all the information required to provide informed consent. If the potential participant understands at least two key written and spoken words, the accessible PIS and consent form should be provided.

The potential participants will be allowed appropriate time (at least 24 hours) to consider their participation. The potential participants should be informed about the potential risks and benefits of the trial, have the opportunity to discuss the trial with family or friends and be able to ask questions with a suitably trained and qualified member of the clinical or research team.

Potential participants will be made aware, during screening and consent, of the importance of complete data and the impact that missing data has on a trial as recommended by Hussain et al. 2022 [33]. The research team will make it clear to the participant the number of visits they will be asked to attend and the assessments that will be completed during these visits prior to obtaining consent and entering them into the trial. Where a participant expresses concern the research team will talk through these concerns and explain why these assessments and/or visits will take place.

Participation is entirely voluntary and choosing not to participate will not negatively influence the potential participant's treatment in any way. The right of the potential participants to refuse consent without giving reasons will be respected. Furthermore, the participant will remain free to withdraw from the trial at any time without prejudicing any further treatment (See Section 9.4 for further details of withdrawal).

Consent should be considered as part of an ongoing dialogue with the participant and should be re-confirmed verbally at each visit and trial procedure.

The original consent form will be filed in the investigator site file (working file), and a second copy will be given to the participants.

If a participant is unable to initial the consent form due to arm function impairment, then they will be asked to mark the consent form (if able) and an independent witness, e.g., a family member or the clinical team not involved in the RICFAST 2 trial, will verify consent by countersigning the form.

Following consent, the participant's details will be recorded and entered on to the trial database. If consent is refused or if the potential participant is not eligible then the reasons for refusal or ineligibility will be requested (but they do not have to provide this if they do not wish to do so), and basic information will be recorded to enable completion of Consolidated Standards of Reporting Trials (CONSORT) diagram to enhance the interpretation of trial results.

The participants' GP will be informed of their participation in the trial.

5.5 Confirmation of eligibility

Eligibility will largely be established prior to the baseline visit through telephone or video screening. However a final check will be undertaken following consent at the baseline visit. This will include the FSS-7 assessment [ref] to determine whether their FSS-7 score meets the inclusion criteria (≥ 4). The PI or other appropriately trained member of the site research team who has been delegated to conduct this activity will also check and confirm eligibility against the criteria list in Section 5.1. Participants will only be randomised (Section 7) once eligibility and informed consent are confirmed.

6. Trial treatment

Participants in the RICFAST 2 trial will be trained (face to face and with access to video explainers) to undertake RIC at home, completing a simple weekly treatment log and symptom diary to determine treatment fidelity (successfully piloted previously). RIC treatment consists of inflating a BP cuff (Accoson TM) around the upper arm to 200 mmHg for 5 minutes followed by 5 minutes of deflation (figure 2). This cycle will then be repeated 4 times in total (40 minutes) to complete a single treatment. We have successfully piloted this cycle protocol [31] and demonstrated excellent tolerability. This will be undertaken alongside usual care. Participants can perform RIC at any time of the day that is convenient to them. Trial research staff will call participants every week to discuss adverse events or issues with treatment and encourage compliance with the interventions and treatment logs. Participants will not be told which pressure is an active arm and will be blinded to allocation group, asked simply to inflate the pressure to the sticker indicated on the pressure cuff (*See appendix – RIC instruction sheet*). These treatments will be in addition to their usual care and will not displace any activity.

HYPERLINK "https://www.google.co.uk/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&uact=8&ved=0ahUKEwjy6JK6wYzYAhWIa5oKHbpqDzMQjRwIBw&url=https%3A%2F%2Fwww.healthline.com%2Fhealth%2Fhow-to-check-blood-pressure-by-hand&psig=AOvVaw3yzmHhzYeL

Figure 2. Remote ischaemic conditioning treatment (RIC).

Participants will be randomised 1:1:1:1 to one of the following four treatment groups.

6.1 Treatment group A (Control)

The **sham (control) group (n=15)** will be asked to inflate the BP cuff around the arm to 50 mmHg, 3 x per week for 6 weeks. This sham protocol successfully blinds participants [34].

6.2 Treatment group B (Regular RIC)

The **regular RIC group (n=15)** will be asked to perform the active RIC treatment 3 times a week for 6 weeks, inflating the cuff to 200 mmHg for each treatment.

6.3 Treatment group C (Intense RIC)

The **Intense RIC group (n=15)** will be asked to perform the active RIC treatment (200 mmHg pressure) 5 times a week for 6 weeks.

6.4 Treatment group D (Long RIC)

The **Long RIC group (n=15)** will be asked to complete the active RIC (200 mmHg pressure) treatment 3 times a week but for 12 weeks.

6.5 Stopping treatment

Participants or clinicians may choose to stop RIC at any time, and reasons will be recorded in the trial database. Participants stopping RIC will revert to usual care (which may be nothing if already discharged from NHS services) but we will continue to obtain follow up data, unless the participant requests complete trial withdrawal.

6.6 Compliance to treatment

Data from intervention treatment logs will provide information on compliance to self-delivered RIC therapy. These data will be reviewed at the weekly check in visits and the face to face follow up visits.

7. Randomisation and enrolment

Participants will be block randomised (1:1:1:1) using an online system (Sealed Envelope Ltd, 2017) to receive one of the four treatment allocations by an independent researcher. Participant randomisation will be stratified by baseline modified Rankin Scale (mRS) score according to dependency (mRS 0-2 and mRS 3-4), and baseline FFS-7 score.

7.1 Blinding

Knowledge of treatment assignment may consciously or subconsciously influence change in behaviour of trial participants and investigators which can bias trial results. Participants who know that they have not received active treatment may be less likely to comply with the research protocol and are more likely to withdraw from the trial. Those aware that they are receiving active treatment may be more likely to provide exaggerated biased assessments of the effectiveness. We cannot also rule out that some participants may psychologically respond positively to active treatment even if the treatment is ineffective due to the placebo effect. Similarly, blinded research investigators may be less likely to focus their attention on participants in the active treatment group and therefore all groups will be given equal attention regardless of allocation.

Participants will be informed they will be receiving one of 4 treatment allocations but will not know which one as all treatments will cause a pressure feeling in the upper arm. While the primary outcomes of this study are feasibility outcomes, we will ensure that follow up assessments are undertaken by a researcher blinded to treatment allocation at all follow up visits.

7.2 Unblinding

In the event of any safety concerns for any participants, unblinding can occur so that clinical teams treating any acute illnesses can assess and manage complications appropriately and the central research team can assess any unexpected or serious adverse events for causality in terms of the intervention.

Participants will be given the opportunity to be unblinded at the end of the trial. This will take place once all data entry and data cleaning has been completed and the final analysis plan has been signed off.

Participants in the Group A (control) will not be offered the opportunity to use active RIC once the trial has ended. This is because we do not know whether it provides any therapeutic benefit.

8. Outcomes

8.1 Primary outcome

Feasibility of the interventions will be based on assessment of safety, acceptability and compliance criteria during the intervention periods:

- **Safety** – no serious adverse events related to RIC.

- **Acceptability** – Likert scale (1= none; 5 = extremely severe) rating of symptoms related to RIC via treatment logs. Less than a third of participants reporting at least moderate discomfort (mean score ≥ 3), as well as from qualitative semi-structured interviews with participants completing the study.

- **Compliance** = > 80% intended treatment sessions completed.

Trial feasibility will be based on assessment of recruitment rates (at least 1.5 participants /month).

8.2 Secondary outcomes (6, 12 and 24 weeks)

Compared to baseline, changes in the following will be measured at 6, 12 and 24 weeks from the start of treatment, unless stated otherwise (*those only assessed at 6 and 12 weeks) to assess short and long-term effects:

Fatigue Severity Scale (FSS-7)

Mean change in FSS from baseline to end of treatment will be recorded. Its validity, reliability, and responsiveness are well established as are CID data [35-37]. Its use has also been recommended by The International Stroke Recovery Round Table [8]. We will measure fatigue at 24 weeks to determine sustainability of any treatment effect to address objective 3.

Modified Fatigue Impact Scale (MFIS)

We will also use the MFIS as a secondary measure of fatigue to characterise fatigue symptom profiles [38] to address objective 5. The MFIS was originally developed to measure fatigue in MS [39], its content validity, internal consistency and test-retest reliability have been demonstrated in stroke populations [40].

Other measures:

- Modified Rankin Score (mRS) [41]
- Barthel index (BI) [42]
- PHQ9 and GAD7 [43,44]
- Stroke Impact Scale (SIS) [45]
- EQ-5D [46]

Improvements in fatigue may also affect function (BI, mRS), mood (GAD-7, PHQ-9) and quality of life (SIS, EQ-5D), and thus these measures will capture such effects.

Measures of Physical Activity

Improvements in fatigue may also affect estimates of aerobic capacity (6MWT*) and physical activity (step count) which are associated with functional capacity

and all-cause mortality. All participants will undergo a Six Minute Walk Test (6MWT) at baseline and end of treatment (EOT), but not 24 weeks. We will also provide each participant with a smart wearable sensor (Google Inspire3 FitBit, Figure 3), that will, subject to the participants explicit consent, record activity data to a WebAPI service through *Google Health UK*, who have committed to providing project support for this study. Participants will be asked to wear the device (on a non-affected arm in the case of hemiparesis) for the duration of the study. They will be asked to ensure adequate charge on the device and wear the device as much as possible including overnight (at least 16hr/day).

For data security purposes each participant will be set up with a generic research google email account to enable activity data to be loaded up onto the WebAPI service without personally identifiable information included. Participants will also be counselled that by agreeing to use the Fitbit device they will be agreeing to the Google/Fitbit terms and conditions and privacy policy.

The following data will be collected on a daily basis for the 24 weeks of study participation:

- Daily Step Count
- Sedentary time
- Distance moved
- Exercise time
- Total estimated sleep time / night



Figure 3. Inspire3 FitBit

8.3 Mechanistic sub-study outcomes

A sub-group of 30 participants (10 from each of groups A, B and C) will be invited to undertake a mechanistic evaluation including inflammatory marker analysis, CPET and MRI 31-Phosphorous Spectroscopy. These will occur at baseline and at the end of treatment (6 weeks).

Inflammatory Marker Analysis

Measures of serum inflammatory markers will be taken to establish if alterations in IL-1beta, IL-6, IL-10, TNFa, heat shock protein, or GLP-1 may mediate effects on fatigue. Exploratory mediation analysis will be performed. Serum and plasma samples from baseline and follow up will be prepared and stored at the Clinical Research Facility, Royal Hallamshire Hospital for analysis altogether when the final sample has been taken and prepared. Analysis will be completed at the University of Sheffield Laboratories.

Cardiopulmonary Exercise Testing (CPET)

Cardiopulmonary exercise testing (CPET) at baseline and 6 weeks will be performed at the Advanced Wellbeing Research Centre, Sheffield Hallam University, and measure peak oxygen consumption ($\dot{V}O_2$peak), ventilatory anaerobic threshold (VAT), and the minute ventilation/carbon dioxide slope (VE/VCO_2). Symptom-limited exercise tests will be conducted using an electronically braked upright stationary cycle ergometer (Lode, Corival) linked to MetaSoft® Studio, supervised by an exercise physiologist. Continuous heart rate (HR; Polar, H10) data will be combined with BP monitoring and breath-by-breath respiratory data collected using a Hans-Rudolph facemask and gas analyser (Cortex Metalyser 3B). The gas analyser is calibrated before each test with standard gas concentrations. An unloaded exercise phase lasting 3 minutes allowed participants to familiarise themselves with resistance-free

pedalling aiming for a cadence of 60 revolutions per minute. A ramp phase then increases workload by 10 Watt per minute. Participants cycle until volitional exhaustion, symptom development (e.g. palpitations, faintness, pallor, confusion, loss of coordination or chest pain) or they were unable to maintain cadence (<50 rpm) [47]. The $\dot{V}O_2$peak reflects the body's maximal capacity to generate energy through aerobic metabolism and is correlated with functional capacity in stroke [48]. During incremental exercise, oxygen uptake ($\dot{V}O_2$) and expired carbon dioxide ($\dot{V}CO_2$) increase linearly until oxidative metabolism can no longer sustain the required workload. At this point, anaerobic metabolism becomes the predominant source of energy production leading to an increase in blood lactate concentration [49]. This is termed the ventilatory anaerobic threshold (VAT), a useful measure of submaximal, sustainable exercise capacity. The V-slope method plotting $\dot{V}O_2$ as a function of $\dot{V}CO_2$ will be used to estimate VAT [50]. The minute ventilation-to-carbon dioxide production (VE/ $\dot{V}CO_2$) slope is an index of ventilatory efficiency and quantifies the ventilatory rate required to eliminate 1 litre of CO_2 [21] and steepens (increases) in people with cardiac or pulmonary disease and with age due to reduced capacity for oxidative metabolism and increased anaerobic glycolysis [50]. We will also measure the Oxygen Uptake Efficiency Slope as an index of exercise performance and cardiopulmonary reserve that requires only submaximal effort [51].

Phosphorous-31 magnetic resonance spectroscopy

Adenosine triphosphate (ATP) is hydrolysed to adenosine diphosphate (ADP) and inorganic phosphate (Pi). During sustained, effortful skeletal muscle contractions, ADP and Pi accumulate, along with hydrogen ions, contributing to skeletal muscle fatigue [52]. It is thought that RIC triggers signalling pathways that enhance mitochondrial electron transport chain function making them more resilient to states of energy (ATP) deficiency [53]. Phosphorous-31 magnetic resonance imaging (^{31}P-MRS) is a non-invasive technique that indirectly assesses tissue metabolism and mitochondrial function. ^{31}P-MRS allows quantification of skeletal muscle ATP in clinical populations [53]. Participants

will undergo ^{31}P-MRS of tibialis anterior of both legs at baseline and at 6 weeks. Methodology has been described in detail previously [54]. In brief, all scans will be conducted at the Academic Department of Radiology, University of Sheffield, at 3 Tesla (3T) using a 31P/1H dual coil for use at 3.0T (Rapid Biomedical GmbH, Rimpar, Germany). Spectra are acquired at rest from the proximal portion of the left and right ankle dorsiflexors encompassing tibialis anterior. Placement of circumferential coil around the tibial tuberosity is cross-checked for each participant to ensure consistency. A pulse-acquire sequence is applied at rest. Spectroscopic data processing will be conducted by a researcher blinded to participant group. Manual phasing and frequency shift of phosphocreatine to 0 ppm is checked visually in all cases to exclude distortions or spurious signals. Signal fitting of 12 resonances is undertaken using the AMARES algorithm (available with jMRUI v6.0, http://www.jmrui.eu) [55]. Resulting amplitudes will be corrected for T1 relaxation using published values [56] and normalised per total phosphorus signal.

8.4 Qualitative outcomes

Semi-structured interviews

Participants will be invited to participate in semi-structured interviews to investigate their experiences of RIC at home. These will be conducted in a quiet and private room, and audio recorded (Olympus digital) so that transcription of the conversation can be undertaken subsequently. Once the recording has been transcribed (using NVIVO software and a password protected University of Sheffield Laptop) it will be deleted. While some quotations will be used, all transcriptions will ultimately be anonymised. We will follow methods detailed by Braun and Clarke [57] in the analysis of the transcripts as follows:

Step 1: Transcription and Familiarisation. The process begins with transcribing the interviews verbatim and immersing oneself in the data. This familiarisation stage involves reading and re-reading transcripts to develop an initial understanding of the participants' experiences.

Step 2: Keyword Selection. This involves selecting keywords based on the principles of realness, richness, repetition, rationale, repartee, and regal. This involves identifying words or phrases that are:

- grounded in the participants' experiences ("realness"),
- offer detailed insight into the phenomenon under study ("richness"),
- appear frequently ("repetition"),
- align with the research's theoretical framework ("rationale"),
- capture poignant moments in the data ("repartee"), and
- are central to understanding the phenomenon ("regal").

Step 3: Coding. Identified keywords are assigned short phrases or words, known as codes, that capture their essence. The codes should be:

- robust, accurately reflecting the data in a theoretical form,
- reflective, demonstrating a link between the data and the theoretical framework,
- relevant, clearly linked to the research question and applied consistently,
- radical, offering unique insights and potentially challenging dominant narratives, and

Step 4: Theme Development. This stage involves grouping the codes into meaningful themes. Themes represent patterned meanings within the data and provide a deeper understanding of the phenomenon under study. The themes should be:

- reciprocal, indicating a mutual connection between the codes that form them,
- recognisable, aligning closely with the original data,
- responsive, addressing the aims and objectives of the research, and
- resourceful, offering valuable insights that contribute to answering the research question.

Step 5: Conceptualisation. In this phase, the themes are interpreted in relation to existing literature on stroke and RIC. This step involves:

- defining the concepts that emerge from the data,
- understanding the relationships between these concepts, and
- positioning the findings within the broader body of knowledge.

We will aim to undertake such interviews until content saturation is achieved.

9. Assessments and procedures

9.1 Baseline assessment

Participants that are eligible and have expressed an interest in participating in the study will be contacted by a researcher to arrange a mutually convenient time to meet. At this initial visit a consent from will be signed and then the FFS-7 completed. If the patient scores equal to or greater than 4 (overall score) they will be eligible to participate in the study. Following this, the researcher will collect baseline sociodemographic and clinical data and will complete baseline assessments including:

- FFS-7

- MFIS
- mRS
- BI
- GAD-7
- PHQ-9
- SIS
- EQ-5D
- 6MWT

If the participant consents to participate in the Mechanistic sub-study, they will require 2 further visits before starting the intervention (CPET and MRI scan). If they are not participating in the Mechanistic sub-study then the researcher will set up the use of the Inspire3 Fitbit and the participant will be randomised by an online block allocation system (Sealed Envelope Ltd. 2017) to one of the 4 treatment allocations. The researchers will then demonstrate how to deliver the intervention and use the symptom diary and treatment log.

The participants will then go home and start the self-delivered treatment intervention. The researchers will organise weekly follow up visits that can be via telephone or video call and if required face to face. These are to check that participants are using the intervention correctly, completing the symptom diaries and treatment logs, and can identify any AEs /SAEs and solve any other issues that crop up.

Data will be collected at the time points listed below. Follow-up time points should be measured from when the participant receives the RIC intervention (the start of treatment). A summary of the data collection time points is provided in Table 1.

9.2 Follow up at 6 weeks (+/- 1 week)

Groups A, B and C will complete their interventions at 6 weeks and be invited back for face to face follow up at Sheffield Teaching Hospitals for the following assessments:

- FFS-7
- MFIS
- mRS
- BI
- GAD-7
- PHQ-9
- SIS
- EQ-5D
- 6MWT
- Adverse events and treatment log review

Data download and analysis of activity measures using the WebAPI will also be undertaken.

For those completing the Mechanistic sub-study they will also undergo in the same week:

- Serum inflammatory markers
- CPET
- 31-Phosphorous MRI Spectroscopy

9.3 Follow up at 12 and 24 weeks (+/- 1 week)

All groups will undergo follow up assessment face to face at 3 and will undergo the following assessments:

- FFS-7
- MFIS

- mRS
- BI
- GAD-7
- PHQ-9
- SIS
- EQ-5D
- 6MWT
- Adverse events and treatment log review

The 6-month assessment can occur remotely as it will involve the same assessments as above excluding the 6MWT. Data download and analysis of activity measures using the WebAPI will also be undertaken at both timepoints.

At the end of the appointment, we will ask participants which group they think they were allocated to.

Table 1. Study schedule

	Remote screening	Face-to-face enrolment appointment*	Baseline scan^	Treatment review	6 week follow up	3 month follow up	6 month follow up
Telephone screening	x	-	-	-	-	-	-
Eligibility form	-	x	-	-	-	-	-
Informed consent form	-	x	-	-	-	-	-
Medical history and examination	-	x	-	-	-	-	-
FFS-7	-	x	-	-	x	x	x
MFIS	-	x	-	-	x	x	x
BI	-	x	-	-	x	x	x
mRS	-	x	-	-	x	x	x
SIS	-	x	-	-	x	x	x
EQ-5D	-	x	-	-	x	x	x
GAD-7	-	x	-	-	x	x	x
PHQ-9	-	x	-	-	x	x	x
6MWT	-	x	-	-	x	x	-
Inspire3 FitBit data download	-	x	-	-	x	x	x
Randomisation	-	x	-	-	-	-	-
Adverse events	-	-	-	x	x	x	x
Participants in the mechanistic sub-study only							
MRI scan			x		x		

Blood sample			x		x		
CPET			x		x		
Adverse events			x		x		

9.4 Unscheduled visits

If it is identified during contact with the participant (either during treatment review calls or through the participant contacting the research team) that there is a problem with the intervention, then they will be invited in for an appointment. This appointment will explore the problem and may involve retraining on how to deliver RIC. The research team will collect information on why the appointment took place and what action was taken during the appointment.

9.5 Participant withdrawals

Participants may wish to withdraw from trial treatment, or there may be a clinical need to withdraw the participant (e.g., the participant experiences another stroke, or a participant becomes pregnant). Participants who discontinue the treatment/intervention will continue to be followed-up and will remain in the trial, unless they request to be withdrawn.

Participants may withdraw their consent for the trial at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/ discontinuation form and in the patient notes, and no further data will be collected for this participant for the trial. Although the participant is not required to give a reason for discontinuing their trial treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the participant at the time of consent.

A participant is defined as having completed the trial when they have completed the 6 month follow up assessments

9.6 Loss to follow-up

Participants will be defined as lost to follow up if they do not complete the 6-month outcome assessments after all attempts to contact them are utilised. If a participant does not complete earlier follow up assessments (at 12 weeks) we will still approach at the 6 month follow up time point.

If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form.

10. Safety Reporting

There have been over 48 clinical trials of ischaemic conditioning in patients with stroke and cerebrovascular disease [58], none of these trials have highlighted concerns over serious adverse events with regards to ischaemic conditioning.

International Council for Harmonisation (ICH) - Good Clinical Practice (GCP) requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

10.1 Definitions

Table 2. Adverse Event and Serious Adverse Event information

Term	Definition

Adverse Event (AE)	Any untoward medical occurrence in a study participant, including those related to the RIC device (Adverse Device event, ADE)
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that: ● Results in death, ● Is life-threatening*, ● Requires hospitalisation or prolongation of existing inpatients' hospitalisation**, ● Results in persistent or significant disability or incapacity, ● Is a congenital anomaly/birth defect, ● Is otherwise considered medically significant by the investigator***.
Related AE/SAE	An AE or SAE which is related to a research procedure.

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Identification

AEs and SAEs are defined as an event that occurs after the participant has been randomised and until completion of their 6 month follow up.

Participants will be asked for details of AEs during the treatment review contacts and during follow up appointments at 6, 12 and 24 weeks.

AEs and SAEs may also be identified by a research nurse, therapist or any other individual, at any point during the trial.

10.3 Recording and reporting

All AEs will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious. An assessment of its relation to RIC will then be undertaken by the PI.

10.3.1 Expected AEs

The following AEs in table 3 are defined as expected in the RICFAST 2 study.

Table 3. Expected AEs

Main clinical trial (RIC)	**Mechanistic Sub-Study**
Skin petechia (AE)	Injury during MR examination related to pacemaker, medical implant or other metallic object (failure of MR safety screening procedures) (AE)
Headache (AE)	
Paraesthesia of the arm (AE)	
Numbness of the arm (AE)	
Discolouration of the arm (AE)	

Upper limb pain / increased upper limb pain (AE)	

10.3.2 SAEs

All AEs classed by the PI or delegate as serious will require more detailed information to be recorded in the participant CRF within one working day from the point of identification.

10.4 Pregnancy Reporting

All pregnancies in trial participants should be reported to the CI and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification. If a participant becomes pregnant during the course of the trial, they will be withdrawn from the trial treatment but will continue to be followed up as per protocol.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the criteria for seriousness, this would be considered an SAE.

Participants who are identified as pregnant during the course of the trial will be followed up by the research team to collect information on the outcome of their pregnancy.

A member of the clinical or research team will attempt to contact the participant around their expected delivery date to enquire about the outcome of the pregnancy (e.g., livebirth, miscarriage) and any congenital abnormality in the newborn identified before or at delivery.

11. Statistics

11.1 Sample size

Experts suggest that between 12 and 20 participants are required per arm of a RCT to demonstrate parameters of feasibility and to estimate the standard deviation of an outcome measure for future power calculations [59,60]. Thus we will recruit 15 participants into each arm.

11.2 Analysis

Simple descriptive statistics will be used to analyse and report intervention and trial feasibility. Exploratory analysis to assess between-group differences for secondary outcome measures will be completed using one-way analysis of covariance using change from baseline adjusted for age, baseline scores, and baseline mRS (≤2/>2) [61], in an intention-to-treat manner. Adjusted mean differences and corresponding 95% confidence intervals will be reported for each time point. Objective 5 will be addressed using fractional polynomials with an interaction term between treatment group and the levels of fatigue type. Pearson correlations between fatigue levels and physical activity data from smart wearables will address objective 6.

12. Trial supervision

The core TMG will meet regularly approximately once every two months but rising to at least once per month as required, for example before key milestones (ethical approval, recruitment initiation etc). The will discuss problems that arise with recruitment and data analysis. The Chief Investigators (AA and AM) will

have overall responsibility for the study and will supervise, monitor and review work undertaken, the data collected and analysis performed.

13. Data handling and record keeping

13.1 Confidentiality

Participant information (socio-demographic, clinical, outcome measure assessment) will be recorded on paper clinical research forms that will be furnished with a study number rather than the patient identifiers. This will then be transferred to an encrypted electronic database stored on a password protected Sheffield Teaching Hospitals research laptop, access to which will be restricted to researchers entering data and performing statistical analyses. Each study participant will be assigned a unique ID number, which will be the only "identifier" linked to data collected. A separate enrolment log will be kept updated by the researcher and held within a study file separate to the study site file. This will link these numbers to the participant's personally identifiable information. In this way, the participants' data will be "pseudo-anonymised" and no identifiable information will be kept with the actual study data.

The research laptop, study site file and enrolment log will be stored in a locked office at Sheffield Teaching Hospitals, Royal Hallamshire Hospital (RHH). Participants will undergo baseline and follow up data collection at the RHH or the AWRC. Rooms there are private and data collection will be conducted in a confidential manner.

13.2 Consent

Patients will only be enrolled in the study if they have capacity to understand the study information sheet and give informed consent. All members of the

research team have undergone GCP training, Participants are free to withdraw from the study at any time without giving a reason and without it affecting their clinical care.

Participants will be free to undergo all other therapeutic activities (e.g. stroke rehabilitation, exercise, psychological therapies) during the study period and will be asked to record this in their study diaries.

13.3 Travel Reimbursement

Participants will be reimbursed expenses of travel to and from scheduled study visits **up to a maximum of £20 per study visit.**

14. Patient & Public Involvement (PPI)

Our ultimate aims are to ensure that people with stroke feel like they are part of the research team and have a real impact in forming the way in which we deliver, analyse and disseminate the study findings.

The Sheffield Stroke Advisory Group (SAG) has worked alongside clinicians from concept inception to completion of the preliminary study and has been instrumental in optimising participant selection and recruitment, intervention delivery and facilitation of outcome measurements. On the 17th April 2023 panel members again worked with clinical academics on developing this proposal including study design, recruitment predictions, and outcome measures including the use of a smart wearable technology to acquire step counts and activity data. To enhance participation of underrepresented minorities they suggested trial literature be translated to other languages e.g. Urdu, Hindi, etc, and production of an explainer video which the panel are keen to help develop to aid inclusivity and diversity in recruitment. We will use the HRA endorsed ‘Staying Connected’ toolkit to ensure transparency and continuous participant

engagement throughout the study. We have strong connections with Darnall Wellbeing, a Sheffield community health organisation located in an area of Sheffield with high ethnic diversity socio-economic deprivation, whose stroke survivors have been very supportive of our study proposal and the potential that RIC may offer.

We ensure that lay members are supported throughout research meetings with briefings and debriefings, allocation of committee members to 'buddy' lay members through tasks e.g., ensuring abbreviations are explained and that information is presented using terminology that all committee members can understand and follow. This ensures maximal participation at study meetings.

15. Equality, Diversity and Inclusion (EDI)

Our Stroke Advisory Group (SAG) includes service users of different ethnic backgrounds and differing impairments (aphasia, cognition, motor, psychosocial) that bring a wealth of lived experience to our research projects. Our research group has also made strong links with Darnall Wellbeing, a not-for-profit community health organisation associated with a GP collaborative in an area of Sheffield with high ethnic diversity and socio-economic deprivation. Collaboration with both groups and has been vitally important in embedding equality, diversity and inclusivity in our study design:

Recruitment: We aim to recruit a representative sample of participants from underserved and hard to reach groups and those disproportionally affected by stroke e.g. Black, South Asian, low socio-economic status. Using the PHIND software to map patient lists with geographical provides an opportunity to post invitations to underserved populations, with the aim of influencing the characteristics of our trial sample and ensuring demographic diversity. By evaluating in real time demographic characteristics of recruited participants,

subsequent mailouts can be adjusted accordingly to target specific geographical areas in which to oversample, based on populations that are underrepresented.

Delivery: Our SAG suggested development of explainer videos for the overall trial activities and the intervention delivery over spoken in the top 3 prevalent languages in Sheffield and Doncaster regions (English, Punjabi, Urdu). They would help researchers develop these materials. A third of stroke survivors have aphasia and easy access materials will be produced to facilitate their participation. The Consent Support Tool communication screening test [ref], developed by members of our research group, will be used to form an individualised prescription of the communication strategies that will aid participant understanding. This will ensure information and support is tailored to the individual throughout trial procedures, the intervention, and outcomes assessments.

16. Publication

Results of the trial will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the trial will also be made available on the University of Sheffield website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The results will be published on a freely accessible database within one year of completion of the trial.

17. Finance

RICFAST 2 is funded by the Stroke Association (project number: PG2S21\100019), with details drawn up in a separate agreement. The views expressed are those of the author(s) and not necessarily those of Stroke Association, NIHR or the Department of Health and Social Care. Use of the WebAPI for analyses of the smart wearable data is supported by Google Health UK.

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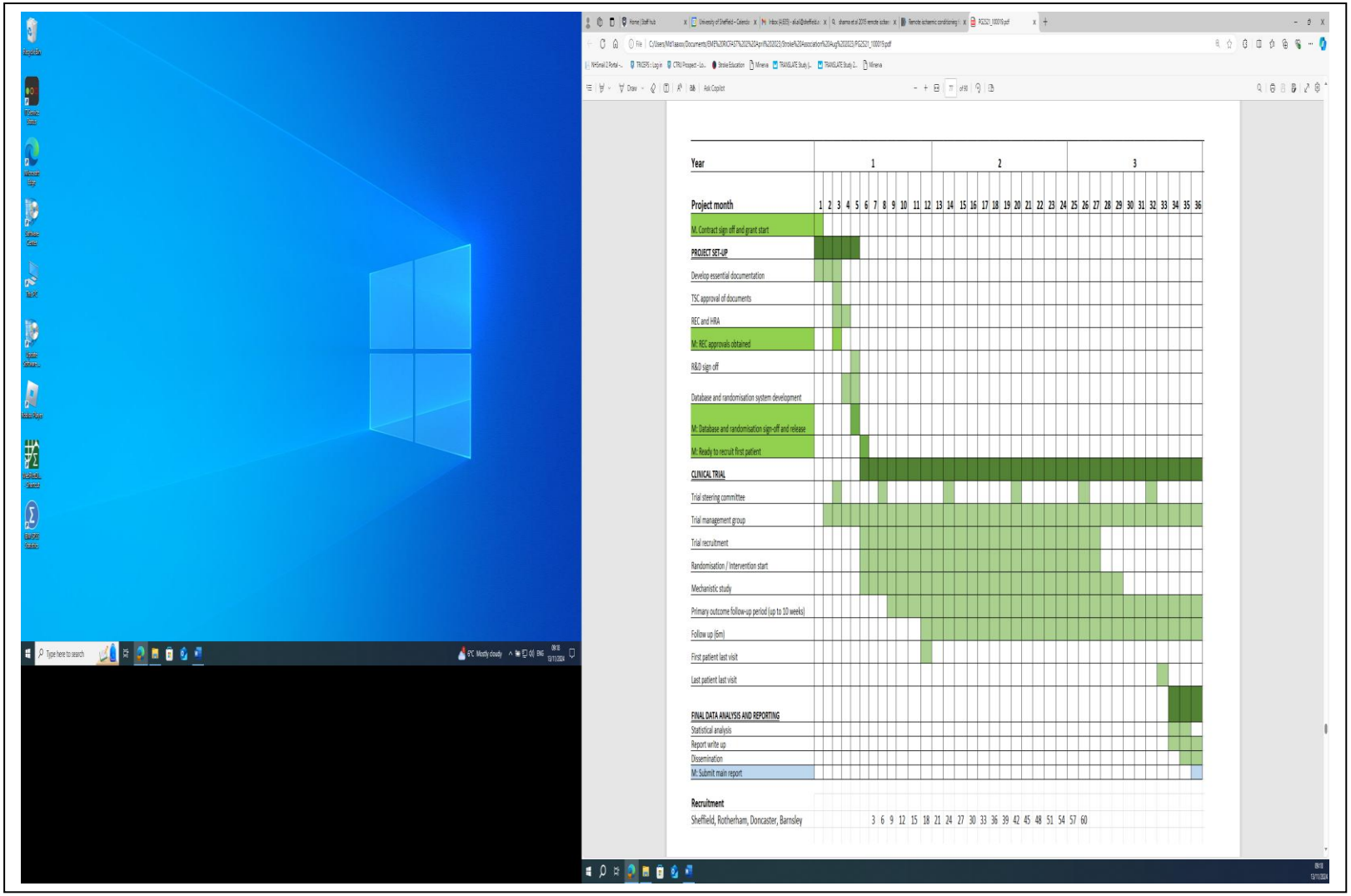
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19. **GANNT**


Year
1
2
3
Project month
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
M: Contract sign off and grant start
PROJECT SET-UP
Develop essential documentation
TSC approval of documents
REC and HRA
M: REC approvals obtained
R&D sign off
Database and randomisation system development
M: Database and randomisation sign-off and release
M: Ready to recruit first patient
CLINICAL TRIAL
Trial steering committee
Trial management group
Trial recruitment
Randomisation / Intervention start
Mechanistic study
Primary outcome follow-up period (up to 10 weeks)
Follow up (6m)
First patient last visit
Last patient last visit
FINAL DATA ANALYSIS AND REPORTING
Statistical analysis
Report write up
Dissemination
M: Submit main report
Recruitment
Sheffield, Rotherham, Doncaster, Barnsley
3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60